REMARKS

Claims 45-48 have been labeled as "withdrawn" in view of the Examiner's withdrawal of these claims in the Office Action. As noted below, Applicant seeks reconsideration and rejoinder of these claims.

Election/Restriction

The Examiner imposed a restriction between claims 36, 39, 40 and 44 and the later-added claims 45-48. The Examiner indicated that a constructive election of claims 36, 39, 40 and 44 was made because these claims were originally presented for prosecution and had received an action on the merits. Applicant respectfully disagrees with and traverses the restriction imposed by the Examiner.

Claims 45-48, added in the previous Amendment, are directed to the use of specific compounds that are generically claimed in claims 36, 39, 40 and 44. The Examiner indicated that the reason that the added claims are directed to a distinct invention from that previously claimed is that "the compounds of claims 36, 39-40 and 44 are inhibitors of MLKs and act at the enzyme level, while the MLK and SEK1 act at the gene level." Office Action at page 2, paragraph 1.

Applicant respectfully disagrees because the Examiner's contention is erroneous. The compounds recited in claims 45-48 are compounds that block ATP binding to MLK by binding to a MLK ATP binding site. They do not "act at the gene level".

Evidence of action at the protein level, rather than the gene level, is provided in the specification as follows.

Evidence pertaining to dominant negative SEK1 is provided in the description of Figures 4, 5, 10, and 11 on pages 7 and 8, which show the effects of the expression of dominant negative

SEK1 protein. See also the paragraph bridging pages 9 and 10, which describes expression of dominant negative SEK1 as an inhibitor of JNK

Evidence pertaining to kinase dead MLK2 is provided in the description of Figures 10, 12, 13, and 14 on page 8, which show the effects of the expression of kinase dead MLK2 protein. See also page 10, lines 24-26, which describes the expression of kinase dead MLK2 protein and its effects on blocking neuronal cell death.

In addition, the description of the MLK and JNK biochemical cascade on page 9, lines 4-14 provides that MLK and JNK proteins bind to SEK1: "The MLK protein directly binds to and stimulates a SEK1 protein which in turn binds to and stimulates JNK." (page 9, lines 8-10)

Because the basis for the Examiner's restriction of the claims is erroneous, Applicant respectfully requests reconsideration and examination of claims 45-48 in the instant application.

Information Disclosure Statement

The Examiner indicated that the Information Disclosure Statement (IDS) filed on January 9, 2002 fails to comply with 37 CFR 1.98(a)(1) because a cover document was filed but no listing of references was attached. Applicant respectfully disagrees.

According to the documents in Applicant's file, a PTO-1449 listing of references was filed along with the IDS on January 9, 2002. A copy of the PTO-1449 document filed on January 9, 2002 is enclosed herewith.

Applicant also submits herewith a new IDS to cite a press release of Cephalon corporation regarding a clinical trial of an MLK inhibitor molecule.

Rejection Under 35 U.S.C. § 112

A. The Examiner has rejected claims 36, 39, 40 and 44 under 35 U.S.C. §112, first paragraph as containing subject matter not adequately described in the specification so as to enable one skilled in the art to practice the invention.

The Examiner alleges that there is "only a hint but no real link" in the application that glutamate-mediated neurotoxicity is a common pathway that contributes to neuronal degeneration in a variety of diseases. Applicant respectfully disagrees.

The participation of glutamate-mediated neurotoxicity (i.e., excitotoxicity) in various neurodegenerative diseases was well known in the art at the time of filing of the instant application. The person of skill in the art would have been aware, as of the filing of the instant application, that excitotoxicity is a common pathway for the action of different neurotoxins, and therefore, that blocking excitotoxicity would be expected to be effective in treating neurodegenerative diseases.

One example of the recognition by persons of skill in the art of the involvement of excitotoxicity in neurodegenerative diseases is an abstract of a presentation given by Dr. F. X. Sureda on April 1, 2000, entitled "Excitotoxicity and the NMDA receptor". In this abstract, Dr. Sureda explains that:

> "Excitotoxicity has been related to several acute neurological disorders, such as epileptic convulsions, in which excitatory synapses become over active. In ischaemic stroke and in post-traumatic lesions, the involvement of excitotoxicity is well established. As mentioned above, in these particular pathological situations a decrease in ATP production evokes glutamate release through depolarisation of presynaptic terminals. In neurodegenerative disorders like Parkinson's or Alzheimer's disease, Huntington's chorea or amyotrophic lateral sclerosis (ALS), a role for excitotoxicity has also been postulated. Moreover, drugs that block NMDA or other glutamate receptors, as well as compounds that decrease glutamate release, attenuate some of the pathological symptoms in experimental models of acute and chronic neurodegenerative diseases." (emphasis added)

A copy of this abstract, found at http://www.eurosiva.org/Archive/Vienna/abstracts/Speakers/SUREDA.htm, is enclosed herewith.

Similarly, publications that refer to the commonality of excitotoxicity in neurodegeneration include, for example, Fornai et al., Neurosci Biobehav Rev. 21(4):401-415, 1997 (experimental parkinsonism prevented by NMDA antagonists); Miranda et al., Neuroscience. 78(4):967-975, 1997 (endogenous excitotoxins implicated in degeneration of dopaminergic neurons in Parkinson's disease, and neuronal protection useful in retarding cell loss in Parkinson's may also be useful in other neurodegenerative diseases in which excitotoxicity plays a role); Olney et al., Exp Neurol. 108(3):269-272, 1990 (excitotoxic processes implicated in degeneration of nigral neurons in Parkinson's disease and striatal neurons in Huntington's disease); Thomas, J Am Geriatr Soc. 43(11): 1279-1289, 1995 (Parkinson's disease, Alzheimer's disease are only some of the neurological disorders in which excitatory amino acids play a major role); Doble, Therapie. 50(4): 319-337, 1995 (animal models suggest that drugs that block glutamatergic neurotransmission might be beneficial in Parkinson's disease, Huntington's disease, and ALS); Utti and Calne, Eur Neurol. 33 Suppl 1: 6-23, 1993 (Parkinson's disease, Alzheimer's disease and ALS result from similar pathological processes).

The foregoing articles mention in their abstracts the commonality of excitotoxicity in a variety of neurodegenerative disorders. Therefore, it is apparent that one of ordinary skill in the art would have been aware of the effects of excitotoxicity in various neurodegenerative disorders as of the time that the instant application was filed.

The specification provides a new target for modulating the effects of excitotoxicity. Thus, the specification clearly indicates to one of ordinary skill in the art, in view of the knowledge possessed by the person of skill in the art, that Applicant was in possession of the claimed invention.

The Examiner also alleged that no guidance was provided as to the selection of "suitable compounds" for testing using Applicant's screening assay. Office Action at page 5. Applicant

respectfully urges the Examiner to reconsider this basis for objecting to the claims. The identification of "suitable compounds", or the use of the screening assay, are irrelevant to the claimed invention. The claims recite the use of compounds that block ATP binding to MLK, which may, but do not need to be, identified using Applicant's screening assay. Applicant also notes that the purpose of a screening assay is to identify compounds that have a certain activity, regardless of structure. Therefore, identification of "suitable compounds" for testing defeats the purpose of a screening assay, at least in part.

The Examiner then appears to sharpen the focus of this aspect of the rejection by stating that "Applicant does not provide any guidance in the way in which to chose [sic] the enzymes in the first place and then fails to provide any guidance in the way in which any point mutations of any enzymes should be made to the ATP binding region." Office Action at page 5. Again, the claims specify the enzymes that are relevant: MLK. Therefore, no choice of enzymes is required of the person practicing the claimed invention. Moreover, the knowledge of the person of skill in the art clearly includes the knowledge that inhibitors of ATP binding inhibit kinase activity. It is an absolute requirement of kinases that they be able to bind ATP in order to transfer a phosphate to and acceptor site on a target protein.

The specification clearly provides a specific point mutation of MLK2 in Example 3, and references a kinase dead MLK3 molecule that was known in the prior art (Tibbles et al., EMBO J. 15:7026-7036, 1996). The specification describes the inhibitory effects of kinase dead MLK2 in Fig. 12 (apoptosis induced by mutated huntingtin blocked), Fig. 13 (apoptosis induced by glutamate or kainic acid blocked), and Fig. 14 (apoptosis induced by APP-C-100 blocked). In addition, Fig. 11 shows the effects of a dominant negative SEK1 molecule in inhibiting apoptosis induced by wild type MLK.

Regarding additional mutations that may be made to MLK to inactivate the ATP binding site (this applies particularly to claims 45-48), one of ordinary skill in the art is very familiar with ATP binding sites and the determination of mutations in such sites to render the ATP binding site inactive. Any experimentation that would be required would be strictly routine.

On page 6 of the Office Action, the Examiner states that the enablement requirement for human therapies is very high, that methods for administering compounds to humans generally require support evidence, and that the specification lacks working examples of treatment. Applicant notes that many patents have issued that claim compounds and their use in treatment, with the basis for the treatment being the biological (in vitro) activity of the compounds. This is essentially what Applicant has provided: the identification of a relevant target (MLKs) for modulating excitotoxicity and therefore treating Parkinson's disease. The person of skill in the art does not need further disclosure for the specification to enable the treatment of Parkinson's disease. The person of skill in the art need only conduct routine experimentation in order to determine appropriate amounts of a compound that blocks ATP binding to MLK that are both safe and efficacious. Such experiments are the domain of the USFDA, not the USPTO.

Based on the foregoing arguments, Applicant respectfully requests that the Examiner withdraw the rejections of claims 36, 39, 40, and 44 under 35 U.S.C. §112, first paragraph.

B. The Examiner has rejected claims 36, 39, 40 and 44 under 35 U.S.C. §112, first paragraph as failing to comply with the written description requirement.

First, the Examiner indicated that the recitation in the claims of compounds that block ATP binding to MLK by binding to a MLK ATP binding site is new matter.

Applicant respectfully disagrees that the amendment to the claims introduced new matter. Applicant provided a description of this in Example 3, which discloses the mutation of the ATP binding site to prepare kinase dead MLK2 (a → g at position 651). Furthermore, the specification (again, Example 3) references a paper by Tibbles et al (EMBO J. 15:7026-7036, 1996) that provides kinase-dead mutants of MLK-3.

One of ordinary skill in the art, in reading the specification, would understand that the specification discloses kinase-dead MLK enzymes that contain mutations in the ATP binding

site. Thus, one of ordinary skill in the art would recognize that Applicant was in possession of the subject matter now claimed.

Second, the Examiner stated that no link is established between the ability of MLK to mediate neurodegeneration in Parkinson's disease and other named diseases (e.g., Huntington's disease, Alzheimer's disease). Applicant respectfully disagrees for the following reasons.

The link between a compound and its use can be supported by that known by one of ordinary skill in the art, since the specification is written for the skilled person. The person of skill in the art would have been aware, as of the filing of the instant application, that excitotoxicity is a common pathway for the action of different neurotoxins, and therefore, that blocking excitotoxicity would be expected to be effective in treating neurodegenerative diseases. For example, see the references mentioned above in connection with the enablement rejection..

Thus, the specification clearly indicates to one of ordinary skill in the art, in view of the knowledge possessed by the person of skill in the art, that Applicant was in possession of the claimed invention.

Rejection Under 35 U.S.C. §103

The Examiner rejected claims 36, 39, 40, and 44 under 35 U.S.C. §103(a) as being unpatentable over Miller et al. (US 6,060,247). Applicant respectfully traverses the rejection and requests reconsideration.

First, the Examiner indicates that Miller teaches an assay for compounds that decrease cell death in which adenovirus constructs that express any of more than 60 gene sequences, or combinations of gene sequence, are used to identify such compounds. The Examiner has selected one of the constructs and indicates that no reason to select the specific MLK construct from among all disclosed is needed because "Miller considers all of the constructs functional equivalents." Office Action at page 9.

Thus Miller does not differentiate among the group of sequences listed at the very end of the patent, does not provide exemplification or experimental details of the use of these sequences, and does not provide guidance for their use. At most, the list of sequences at the end of the Miller patent is an invitation to the person of skill in the art to experiment. However, because the assays provided by Miller may identify compounds that are useful for treating neurodegenerative disease, or (by virtue of their toxic effects on neurons) for treating cancer or as pesticides, the skilled person would not know which of the many sequences listed should be used to identify compounds that may be used as therapeutics for treating neurodegenerative disease. Therefore, the skilled person cannot have had a reasonable expectation of success in randomly picking from among allegedly equivalent genes and using the selected sequence to identify compounds useful for treating neurodegenerative diseases.

Second, Miller qualifies the statements regarding the use of the compounds found using the assays. Miller states that the assays "can be used to test for compounds that decrease cell death and/or stimulate cell growth and hence may have a therapeutic value." Miller, col. 7, lines 31-33. Such qualification does not provide one of ordinary skill in the art with a reasonable expectation of success, since the use of the assays, and the compounds identified using the assays, if any, are only possibly of therapeutic value.

Third, the Examiner also states that the claim limitation that Applicant added previously (compound used in method blocks ATP binding to MLK) was "not probative because it is new matter." Office Action at page 9. Applicant respectfully disagrees.

As described above in the response to the rejections under 35 U.S.C. 112, first paragraph, Applicant's amended claims do not include new matter. Applicant notes that the Examiner has not indicated any portion of Miller that teaches the use of any such compound.

In addition, the Examiner offers no substantiation of a reasonable expectation of success that one of ordinary skill in the art would expect in practicing Miller's technology. Miller offers a laundry list of gene sequences in adenovirus constructs, but describes no results with the

construct encoding MLK that might give one of ordinary skill in the art the reasonable expectation of success needed for making a *prima facie* case of obviousness.

This issue alone is sufficient to cause the rejection to fail. Without a reasonable expectation of success, one of ordinary skill in the art would not attempt the combination of steps suggested by the Examiner. In particular, because (according to the Examiner) Miller considers "all of the constructs functional equivalents" (Office Action at page 9), there would be no motivation to select the only one from the long list offered by Miller. Contrary to the Examiner's view that this statement by Miller negates the need for an explicit teaching to provide a reasonable expectation of success, Miller's statement requires more. It requires that Miller teach in some other way that one of ordinary skill in the art should select MLK-adenovirus constructs and use them in Miller's method.

Applicant further notes that the Miller patent does not establish any explicit link between MLK and Parkinson's disease, as admitted by the Examiner: "A specific linkage to MLK and Parkinson's was not established." Office Action at page 10, lines 11-12. This means that Miller does not provide an adequate written description of this linkage (according to the Examiner's reasoning applied in rejecting Applicant's claims as lacking in written description), such that the Miller patent is not adequate to support the rejection. One of ordinary skill in the art would not understand from a reading of the Miller patent that Parkinson's disease could be treated by modulating MLK activity, nor would that person be motivated to investigate the effects of MLK in Parkinson's disease.

Based on the arguments presented above, Applicant respectfully requests that the Examiner withdraw the rejection of claims 36, 39, 40, and 44 under 35 U.S.C. §103(a).

CONCLUSION

In view of the foregoing amendments and remarks, this application should now be in condition for allowance. A notice to this effect is respectfully requested. If the Examiner

believes, after this amendment, that the application is not in condition for allowance, the Examiner is requested to call the Applicant's attorney at the telephone number listed below.

If this response is not considered timely filed and if a request for an extension of time is otherwise absent, Applicant hereby requests any necessary extension of time. If there is a fee occasioned by this response, including an extension fee that is not covered by an enclosed check, please charge any deficiency to Deposit Account No. 23/2825.

Respectfully submitted,
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